

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICANT(S) : Mueller-Walz, CONFIRMATION. NO.: 5874  
SERIAL NUMBER : 10/574,334 EXAMINER : Kennedy, Nicoletta  
FILING DATE : March 7, 2007 ART UNIT : 1611  
FOR : AEROSOL FORMULATIONS COMPRISING FORMOTEROL FUMARATE  
DIHYDRATE

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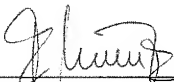
Via EFS

**DECLARATION UNDER 37 C.F.R. § 1.132**

I, Rudi Mueller-Walz, Ph.D., declare:

1. I am currently Head of Inhalation Formulation and Process Development at SkyePharma, A.G. In this position I am responsible for development of inhaled dosage forms and device development. My *curriculum vitae* is already of record in this case.
2. The data in Exhibit A presents comparative stability data for two aerosol suspension formulations of formoterol fumarate dihydrate ("FFDH") following 12 months of storage. The formulations are identical except for their water content. The formulation labeled "Dry" has an FFDH water content of 4.42%. The formulation labeled "Wet" has an FFDH water content of 5.11%. Water content was measured by the Karl Fischer method, a standard analytical tool for measuring the water content of a sample.
3. The "dry" formulation was obtained by vacuum drying the FFDH raw material at max. 0.1 bars and 38 to 42°C. The "wet" formulation was obtained by storing the FFDH raw material for 1 week at very high ambient humidity.
4. Two properties of the formulations were measured, the dose uniformity through container life and the aerodynamic particle size distribution of the delivered dose, specifically the fine particle fraction (FPF), which is the inhalable part of the delivered dose of the aerosol.
5. The data in the first two rows shows that the Mean delivered dose for the dry formulation was 8.46 µg with a relative standard deviation (RSD) of 11.72%. In contrast, the wet formulation delivered a dose of only 6.83 µg with a much higher RSD of 19.21%. These data demonstrate that the wet formulation had a substantially better dose uniformity compared to the dry formulation.

6. Next, the data shows the aerodynamic particle size distribution for a 6  $\mu\text{g}$  dose of FFDH, using the average value of two puffs from a metered dose inhaler. The fine particle dose for the dry formulation was 5.75  $\mu\text{g}$  with an RSD of 2.31%. In contrast, the fine particle dose for the wet formulation was only 3.97  $\mu\text{g}$  with an RSD of 3.9%. Thus, the dry formulation delivered a substantially higher fine particle dose than the wet formulation.
7. Taken together, these data demonstrate the improved stability of the "dry" aerosol suspension FFDH formulation in which the FFDH was dried to lower its water content to 4.42% water as compared to the same formulation that was not subjected to a drying step and retained a water content of 5.11%.
8. As a person signing below, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, United States Code, § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Declarant's Signature  
Full Name of Declarant: Rudi Mueller-Walz, Ph.D.

14/ Dec / 2011

Date

Submitted Herewith:  
Exhibit A

## Exhibit A

### Stability of formoterol fumarate formulations after 12 months

	"Dry" (water content of formoterol fumarate di-hydrate = 4.42%)	"Wet" (water content of formoterol fumarate di-hydrate = 5.11%)
<b>Dose uniformity through container life</b>		
Mean delivered dose ( $\mu\text{g}$ )	8.46	6.83
Relative standard deviation (RSD) (%)	11.72	19.21
<b>Aerodynamic particle size distribution</b>		
Fine particle dose ( $\mu\text{g}$ ) (n=2 puffs)	5.75	3.97
Relative standard deviation (RSD) (%)	2.31	3.9

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